On the Synthesis and Reactivity of 2,3-Dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-ones

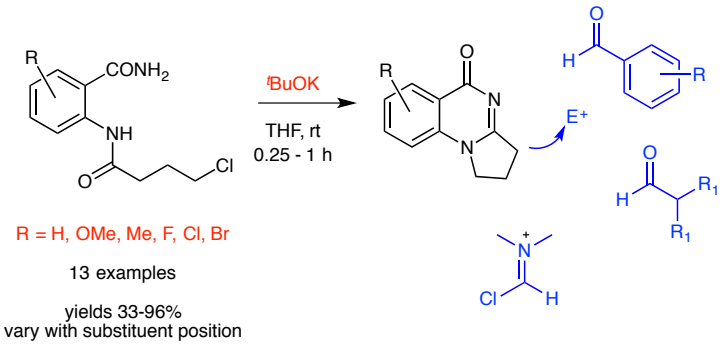
Charlotte L. Sutherell[a,b,1,*]
Steven V. Ley[a]

[a] Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, U.K

[b] Cancer Research UK Cambridge Institute, Li Ka Shing Centre, University of Cambridge, Cambridge, CB2 0RE, U.K.

c.sutherell@imperial.ac.uk

Dedicated with respect and best wishes to our friend Dieter Enders on the occasion of his 70th birthday.



Received:
Accepted:
Published online:
DOI:

Abstract An improved, scalable synthetic route to the quinazolinone natural product 2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one is reported. The applicability of this method to analogue synthesis and the synthesis of related natural products is explored. Finally, reactivity of the scaffold to a variety of electrophilic reagents, generating products stereoselectively, is reported.

Key words quinazolinone, alkaloid, 2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one, deoxyvasicinone

Quinazolinone alkaloids are commonly found as the structural basis of natural products and pharmaceuticals that display biological activities in diverse areas, including cancer, CNS systems, inflammation, and hypertension.[2,3] Many quinazolinone alkaloids contain the quinazolinone ring fused with pyrrole or piperidine rings.[4] These are often derivatives of deoxyvasicinone (**1**) or vasicinone (**2**), isolated from *Adhatoda vasica*, and mackinazolinone (**3**), isolated from *Mackinalaya* species (Figure 1).[5,6] These alkaloids have been extensively studied and a wide variety of routes for their synthesis, and of their derivatives, have been developed.[4]

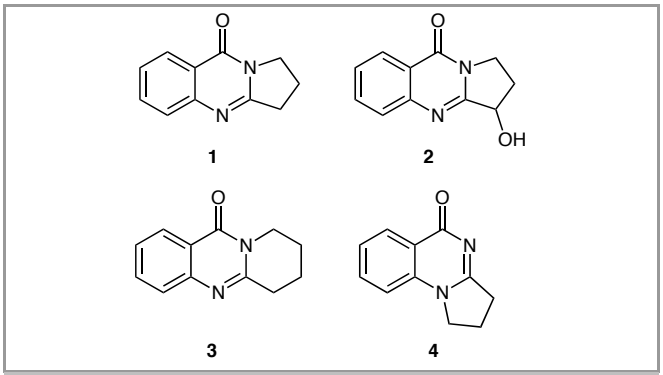
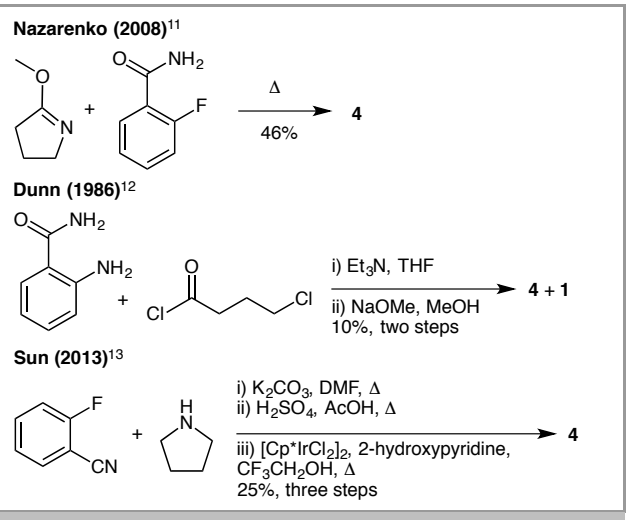


Figure 1 Quinazolinone alkaloids with fused pyrrole or piperidine rings demonstrate a variety of biological activities

2,3 Dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one (**4**), an isomer of deoxyvasicinone (**1**), was only isolated as a natural product in 2015, from *Castanea crenata* Sieb (Chestnut honey).[7] It has, however, been obtained by synthetic methods for much longer.[8] The biological activities of **4** and derivatives based on its alkaloid core have not been extensively investigated compared with related alkaloids **1** and **2**. A brominated derivative of **4** has some antibacterial activity at μg/mL levels against *Bacillus subtilis* and fungicidal activity against *Candida albicans* and *Aspergillus niger*.[9] Compounds containing a core 2,3 dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one motif were found to be inhibitors of proteins in the bromodomain family of epigenetic reader proteins.[10]

In order to fully explore the potential of compound **4** as a scaffold for pharmaceutical or agrichemical applications a robust, readily adaptable synthetic route to **4** and related analogues would be useful. Alkaloid **4** has been synthesized through several methods (Scheme 1). However, some of these routes were low yielding or would be unsuitable for analogue synthesis due to the starting materials or reagents used.[11–14]

Furthermore, work has not been extensively undertaken to test the reactivity of the scaffold and explore its chemistry in comparison to the related deoxyvasicinone **1**. In this paper we report the development of an improved synthetic route to **4**, exploration of the scope of the route, and investigations into the reactivity of **4**. Our synthetic route, based on the existing synthesis by Dunn *et al.*,[12] enabled the reliable and rapid preparation of **4** at reasonable scale and with good yields. Our strategy uses inexpensive reagents and was found to be readily adaptable for the synthesis of analogues and some related compounds. With a route that generated **4** in appreciable quantities, we also investigated the reactivity of the scaffold, highlighting the weakly nucleophilic characteristics of the core.



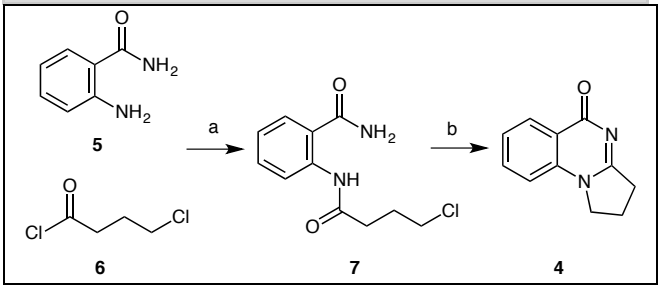
Scheme 1 Summary of some existing synthetic routes to 2,3 dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one **4**

Optimisation of a synthesis to 2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one, 4

The route to 2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one reported by Dunn *et al*. was chosen for exploration, since it used readily accessible, inexpensive reagents and we proposed it would be able to tolerate substitution.[12] In agreement with the literature procedure, reaction of anthranilamide **5** with acid chloride **6** gave the precursor secondary amide **7**. Cyclisation using sodium methoxide gave the two isomers deoxyvasicinone **1** and the desired compound 2,3-dihydropyrrolo[1,2-a]quinazolin-5(1H)-one **4** in low yields comparable to those reported (Table 1).

We proposed that yields might be improved by use of a stronger base. Reaction of secondary amide **7** with two equivalents of potassium *tert*-butoxide (^{t}BuOK) in THF led to rapid cyclisation, with some reactions complete in less than 10 minutes. A significant switch in product distribution was observed, with more of the desired isomer **4** rather than **1** being produced, and the overall yield was also greatly increased. Another strong base, NaHMDS, also demonstrated this effect, but ^{t}BuOK was used subsequently due to its lower cost and ease of use.

Table 1 Optimisation of Reaction Conditions for the Cyclisation of **7** to **4**[a]



Entry	Base	Eq.	Time	Yield **4**(%)	Yield **1** (%)
1	25% wt NaOMe	10	4.00	13	19
2	^{t}BuOK	1	4.00	35	22
3	^{t}BuOK	2	0.25	77	15
4	^{t}BuOK	3	0.25	59	29
5	NaHMDS	2	0.25	71	24

[a] Reaction conditions: (a) Et_3N (2.0 eq), THF, 0 °C to rt, 12 h, 92%; (b) base (equivalents), THF, time.

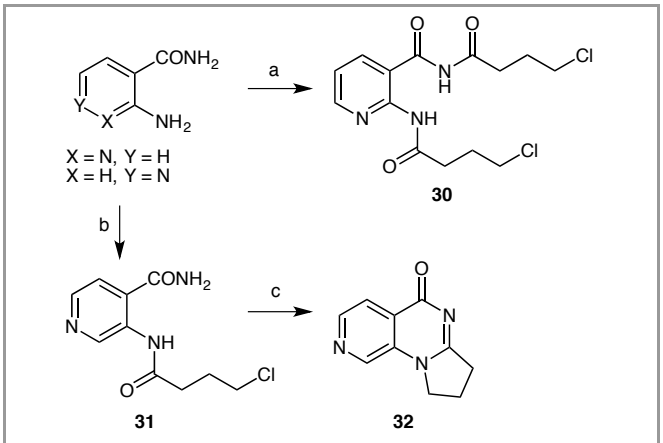
The two isomers could be separated readily by flash column chromatography (FCC) rather than using a Soxhlet extractor as reported.[12] Identification of the isomers was confirmed by the presence of a strong nOe signal in **4** between the aromatic ring and pyrrole ring as well as the large difference in their melting points. The reaction was also performed on a gram scale, using **7**, with yields up to 69% being reliably obtained on this scale.

Versatility of the synthetic route for analogue synthesis

An advantage of this route was the accessibility of substituted 2-aminobenzamides, enabling the robustness of the route for analogue synthesis to be tested. A range of substituted 2-aminobenzamides were obtained through a variety of routes,[15–17] of which microwave assisted hydrolysis from 2-aminobenzonitriles proved the most versatile and reliable method (see Supporting Information).[18] These 2-aminobenzamides were then reacted with acid chloride **6** as before (Table 2). Open chain intermediates **8**-**18** could be accessed in moderate to excellent yields, with a variety of substitution patterns being tolerated, although substitution *ortho* to the amine was low yielding for steric reasons.

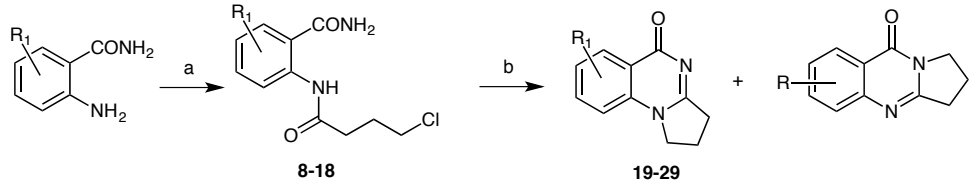
These secondary amides were then reacted with ^{t}BuOK and cyclised successfully with good functional group tolerance. However, the yields and ratio of isomers obtained were sensitive to substitution pattern. Substitution *meta* to the secondary amide generally gave the best yields and the most favourable isomer distribution for the desired 2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one products. For example, on cyclisation of chlorinated intermediate **17** the desired product **28** was obtained in 91% yield after FCC, and none of the alternative isomer was detected by crude NMR..

The methodology was also tested with electron poor systems, and the nucleophilicity of the primary amine was found to be a key determinant of reactivity. Reaction of 2-aminonicotinamide failed to give the desired product; instead compound **30**, product of the reaction of both the primary amine and the primary amide, was isolated (Scheme 2). By contrast, 3-aminonicotinamide could be successfully reacted to give **31**, as the electron-withdrawing group was not in direct



Scheme 2 Use of electron poor nicotinamides to generate analogues of **4**. Reaction conditions: (a) 4-chlorobutanoyl chloride (1.2 eq), Et_3N (2.0 eq), THF, 0 C to rt, 21%; (b) 4-chlorobutanoyl chloride (1.5 eq), Et_3N (1.5 eq), THF, 0 C to rt, 12 h, 58%; (c) ^{t}BuOK (2.0 eq), THF (0.1 M), rt, 2 h, 31%.

Table 2 Synthesis of substituted 2-aminobenzonitriles and subsequent reaction with 4-chlorobutanoyl chloride and cyclisation to give analogues of **4**



8-18 **19-29**

Entry	R	Compound Number	Yield **8-18**	Compound Number	Yield **19-29**	Yield alternate isomer[c]
1	3-Me	**8**	39	**19**	53	26
2	4-Me	**9**	94	**20**	74	11
3	5-OMe	**10**	52	**21**	20	15
4	5-Me	**11**	79	**22**	37	8
5	5-F	**12**	93	**23**	33	6
6	5-Cl	**13**	81	**24**	65	24
7	6-OMe	**14**	79	**25**	82	-
8	6-Me	**15**	60	**26**	90	<4
9	6-F	**16**	94	**27**	73	<5
10	6-Cl	**17**	93	**28**	96	<1
11	6-Br	**18**	78	**29**	88	<5

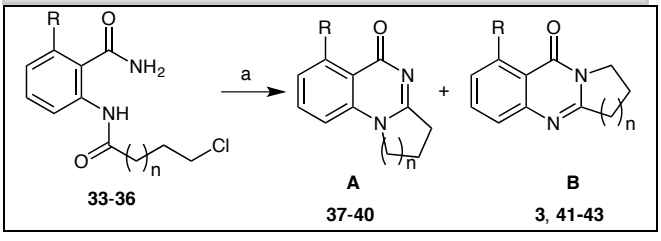
[a] 4-Chlorobutanoyl chloride (1.2 eq), Et_3N (2.0 eq), THF, 0 °C to rt, 4 h to 24 h; [b] ^{t}BuOK (2.0 eq), THF (0.1M), 1 h; [c] Yields were determined on the basis of a crude NMR and subsequent purification of the major product.

conjugation with the primary amine. This amide was then successfully cyclised to compound **32** in 31% yield.

Generation of expanded ring analogues

Analogues of the scaffold with an expanded aliphatic ring system, such as mackinazolinone **3**, have been synthesised previously using the methods of Dunn,[12] Sun,[13] and Jones[14] as highlighted in Figure 1, amongst many others.[4] We assessed whether our improved synthetic route would be applicable to these systems. Pre-cursor compounds **33** and **34** were synthesised using the appropriate acid chloride in 79% and 86% yield respectively. Cyclisation of **33** with ^{t}BuOK led to mackinazolinone (**3**) in 92% yield, rather than the isomer analogous to **4**. Similarly, compound **34** gave **41** in 52% with no isolation of **38** (Table 3). However, substitution of the aromatic ring affected the product distribution. Unlike the unsubstituted system, cyclisation of chlorinated amide **35** bearing a chlorine group gave access to both isomers **39** and **42** in yields of 51% and 48% respectively. However, cyclisation of **36** gave only compound **43** in 20% yield.

Table 3 Synthesis of analogues with expanded ring systems[a]



33-36 **A** **37-40** **B** **3, 41-43**

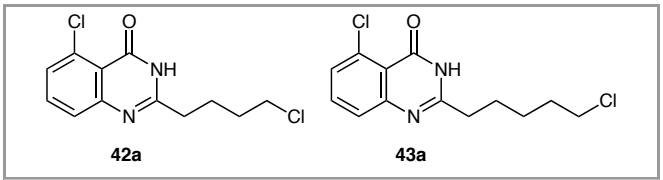
Entry	R	n	Starting material	Product A	Yield (%)	Product B	Yield (%)
1	H	2	**33**	**37**	0	**3**	92
2	H	3	**34**	**38**	0	**41**	52
3	Cl	2	**35**	**39**	51	**42**	48
4	Cl	3	**36**	**40**	0	**43**	20

[a] ^{t}BuOK (2.0 eq), THF, rt

Proposed mechanism

All these observations taken in combination agree with the report that the system can be cyclised through two competing mechanisms.[19] We suggest that use of stronger bases, such as ^{t}BuOK, favours deprotonation of the secondary amide in **7** followed by 5-*exo-tet* cyclisation and subsequent condensation of the lactam with the primary amide (route A). However, when the chain length increases the lactamization is slower. Instead, the condensation of the primary amide onto the secondary amide in **7** may occur first followed by subsequent cyclisation (route B). As these routes would be in competition, their relative rates determine product distribution.

Changing the electronics of the ring will affect both the acidity of the secondary amide and the electrophilicity of the primary amide, altering the ratio of isomers produced. No lactam intermediates from proposed route A were isolated. However, with chlorinated substrates **35** and **36**, with longer chain lengths, reactions were stopped prior to completion, and intermediates **42a** and **43a** could be isolated in 9% and 95% yield respectively, providing some evidence for the existence of route B (Figure 2).



42a **43a**

Figure 2 Intermediates in the cyclisation of longer chain amides that could be isolated

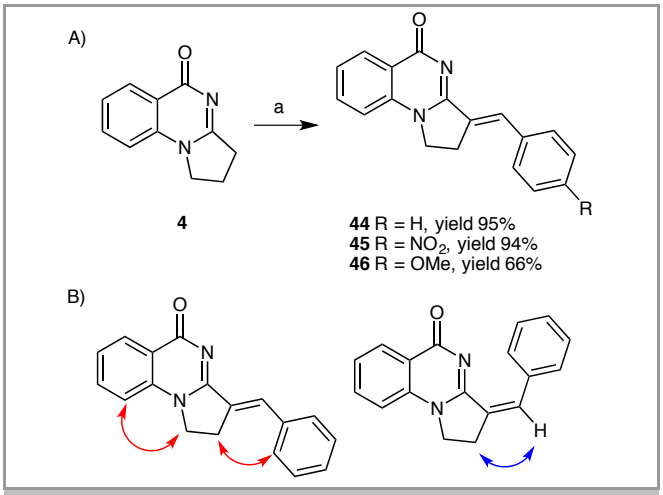
C-Nucleophilicity of the 2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one scaffold

2,3-Dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one **4** is closely related to the alkaloid deoxyvasicinone **1** and, like deoxyvasicinone, shows reactivity towards electrophilic reagents at the C3 carbon position.[20] In studies of the scaffold as

the basis for polymethine dyes, **4** was shown to react with conjugated aldehydes and condensed with benzaldehyde.[12,21] We conducted initial investigations into the extent of this reactivity using a variety of electrophilic reagents to generate a series of substituted derivatives of compound **4**.

Reaction with aromatic aldehydes

The reaction of **4** with aromatic aldehydes was studied first. As reported, heating alkaloid **4** with benzaldehyde with acetic acid and sodium acetate led to rapid condensation and formation of the alkene **44** (Scheme 3).[12] None of the intermediate aldol product was isolated, likely due to the stability of the highly conjugated product. Only one stereoisomer, **44**, was obtained in 94% yield and given the thermodynamic conditions used, the *E* geometry was proposed to be favoured. This was confirmed by nOesy experiments; a distinctive interaction between the condensed aromatic ring and the aliphatic ring was observed, whilst the potential interaction between the alkene proton and ring in proposed *Z* isomer were not identified (Scheme 3B). The methodology was applicable to substituted aldehydes: both electron withdrawing and electron donating groups were tolerated to give the final products **45** and **46** in 94% and 66% yield respectively. The solubility of these products in both organic and aqueous solvent was low.



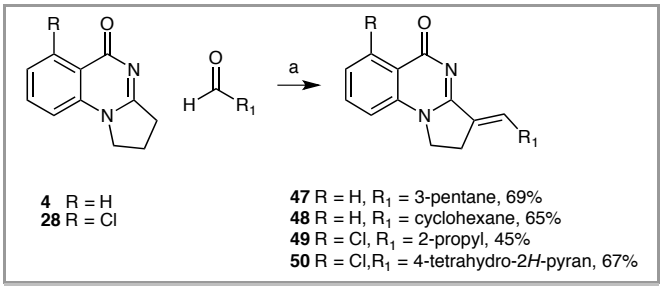
Scheme 3 A) Reaction of **4** with aromatic aldehydes. Reaction conditions: (a) aromatic aldehyde, NaOAc, AcOH, 110 °C, 6 h. B) Proposed characteristic nOes in **44** and its alternative *Z* isomer.

Reaction with aliphatic aldehydes

Unlike aromatic aldehydes, refluxing aliphatic aldehydes with 2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one **4** in acetic acid gave an inseparable mixture of unidentified products. However, treatment of the scaffold with ^{t}BuOK to form an extended enolate and subsequent addition of 2-ethylbutyraldehyde at room temperature led to aldol reaction and then E1cb elimination of water, to give **47** as the *E* isomer in 69% yield (Scheme 4). The chemistry tolerated functionalization of the aromatic ring and varied aldehydes, for example in synthesis of compound **49** and **50**. In some cases the intermediate aldol products could be isolated as a 1:1 mixture of diastereoisomers.

Reaction with formamides

Analogous to reported reactions with deoxyvacisinone,[22] scaffold **4** was reacted with phosphoryl chloride in

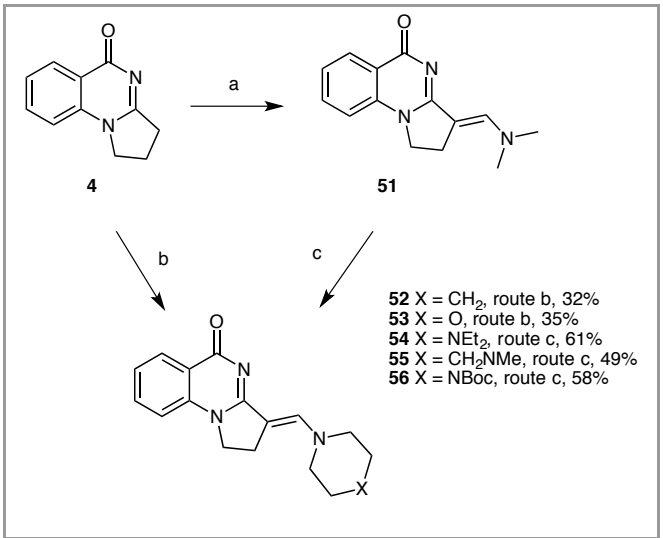


Scheme 4 Reactions of 2,3-dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-ones with aliphatic aldehydes. Conditions: (a) ^{t}BuOK, CH_2Cl_2, 10 min, then aldehyde.

dimethylformamide at 60 °C in a Vilsmeier-Haack style formylation, giving the dimethylaminomethylene derivative **51** in 74% yield (Scheme 5). The *E* isomer alone was observed under the thermodynamic control of these reaction conditions. No aldehyde product from imine hydrolysis was observed, likely due to the stability of the conjugation of the dimethylaminomethylene system once formed.

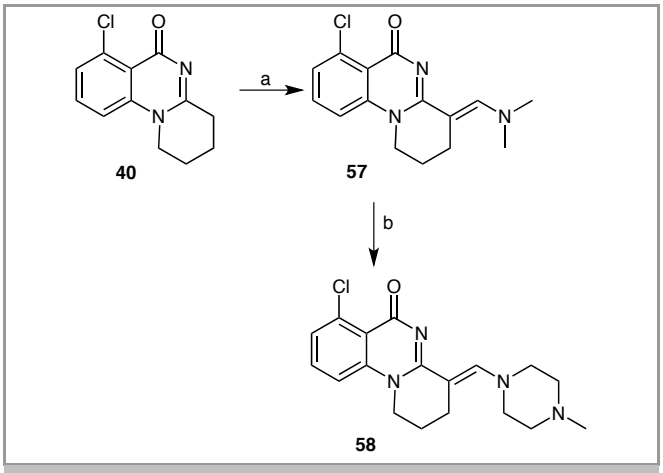
The chemistry could be extended to other simple formamides to give aminomethylene derivatives such as **52** and **53** in moderate yield. Formamides containing additional nitrogen groups such as 1-methylpiperazine did not give products using these conditions. The dimethylaminomethylene product **51** was weakly reactive to nucleophilic substitution, allowing further elaboration of the dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one core. Upon refluxing with excess secondary amine and catalytic DMAP, the dimethyl group in **51** could be displaced giving compounds **54**-**56**.

Ring-expanded analogues such as **39** could also be reacted using this methodology to give derivatives **57** and **58** in 48% and 89% yield respectively (Scheme 6).



Scheme 5 Reaction of **4** and related analogues with formamides and amines. Conditions: (a) $POCl_3$, DMF, 70 °C, 3 h, 74%; (b) formamide, $POCl_3$, CH_2Cl_2, 50 °C, 3-48 h; (c) amine, DMAP, EtOH, 70 °C, 24-96 h

These reactions indicate the reactivity of the 2,3 dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one core to a variety of electrophiles is comparable to deoxyvasicinone **1**. The latter can be brominated and oxidised, and other similar reactivity may also applicable to **4**. In these reactions nucleophilicity was only



Scheme 6 (a) $POCl_3$, DMF, 70 °C, 6 h, 49%; (b) 1-methylpiperazine, DMAP, EtOH, 70 °C, 6 h, 89%

observed at carbon 3. When this position is blocked, for example in isoindolo[2,1-*a*]quinazoline-5-ones,[23] carbon 1 directly adjacent to the nitrogen becomes the most reactive to electrophiles.

In conclusion, a versatile, scalable synthetic route to the 2,3 dihydropyrrolo[1,2-*a*]quinazolin-5(1*H*)-one **4** has been optimised, and shown to be suitable for the synthesis of a variety of analogues and some related compounds. The nucleophilic reactivity of **4** and analogues has been demonstrated with a variety of electrophiles. Condensation with electron-poor and electron-rich aromatic aldehydes occurs in acidic medium whilst aliphatic aldehydes can be reacted under basic conditions, in both cases stereoselectively. Additionally, **4** has been derivatised using Vilsmeier condensation chemistry, and the products of this reaction such as **51** can be used to access other compounds through nucleophilic displacement. These results enable the synthesis of a wider variety of structures based on **4** than previously demonstrated, allowing their chemical and biological activity to be explored.

The experimental section has no title; please leave this line here.

All reactions were performed using oven-dried glassware (200 °C) under a dry argon atmosphere unless otherwise stated or aqueous reagents were employed. All solvents used in reactions were dried and distilled according to standard protocols. All reagents were used as supplied or purified using standard procedures as necessary.

Flash column chromatography (FCC) was performed using Sigma Aldrich silica gel pore size 60 Å, 230 – 400 mesh under air pressure. The solvents used for FCC were distilled before use. "Hexanes" refers to petroleum ether distillate (boiling point – 40-60 °C). Analytical thin layer chromatography (TLC) was performed using silica gel 60 F_{254} pre-coated glass-backed plates and visualised by ultraviolet radiation (254 nm), potassium permanganate or ninhydrin as appropriate. Preparative TLC was performed using silica gel GF 500 micron UNIPLATES (Analtech).

^{1}H NMR spectra were recorded on Bruker Avance DPX-600 (600 MHz), Bruker DPX-400 (400 MHz) or Bruker DCH Cryoprobe (500 MHz). High resolution mass spectrometry (HRMS) was performed on a Waters Micromass LCT Premier spectrometer using electrospray ionisiation and Micromass MS software, or on a ThermoFinnigan Orbitrap Classic using positive ion electrospray. Infrared spectra were recorded as thin films on a Perkin-Elmer Spectrum One FTIR spectrometer. Melting points were collected using a Stanford Research Systems Optimelt automated melting point system using a gradient of 1 °C per min.

Procedures

*Synthesis of 2-(4-chlorobutanamido)-benzamides: general procedure **A***

A solution of the appropriate substituted 2-aminobenzamide (1.0 eq) in THF (2.5 mL per mmol substrate) was cooled to 0 °C and triethylamine (2.0 eq) then the appropriate acid chloride (1.2 eq) in THF (2 mL per mmol substrate) were added to the stirred solution. The reaction was stirred at room temperature until completion as indicated by TLC, when the mixture was diluted with EtOAc and quenched with $NaHSO_4$ (20 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL), combined organic phases dried over $MgSO_4$, excess solvent removed *in vacuo* and the residue purified by FCC.

*Synthesis of 2,3-dihydropyrrolo[1,2-a]quinazolin-5(1H)-ones: general procedure **B***

To a solution of the appropriate substituted 2-(4-chlorobutanamido)-benzamides substrate (1.0 eq) in THF (10 mL per mmol substrate) was added ^{t}BuOK (2.0 eq). The reaction was stirred at room temperature until TLC indicated completion, then solvent was removed *in vacuo*, the resulting residue re-dissolved in CH_2Cl_2 (20 mL) and $NaHCO_3$ (15 mL), and the aqueous layer extracted with CH_2Cl_2 (5 × 20 mL). The combined organic phases were dried over $MgSO_4$ and solvent removed *in vacuo*. The products were obtained after purification of the residue by FCC.

Characterisation data for selected compounds are reported below. For other analogues please see further data in supporting information.

Deoxyvavsicinone (**1**)

To **7** (120 mg, 0.500 mmol, 1.0 eq.) was added NaOMe (25% wt in MeOH, 1.14 mL, 5.00 mmol, 10.0 eq.) and the reaction then heated at reflux for four hours. The reaction was cooled, diluted with CH_2Cl_2 (10 mL), quenched with $NaHCO_3$ (10 mL), the layers separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, and excess solvent removed *in vacuo*. Purification by FCC (2% MeOH/CH_2Cl_2 to 5% MeOH/CH_2Cl_2) gave deoxyvavsicinone **1** (17.7 mg, 0.0951 mmol, 19%) as an off-white solid; mp 105–106 °C, lit. 105–107 °C;[24].

IR (neat, ν_{max}): 2960, 2925, 1671, 1619, 1611, 1465, 1384, 771, 694 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.27 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.72 (ddd, *J* = 8.2, 7.2, 1.5 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.44 (ddd, *J* = 8.0, 7.2, 1.1 Hz, 1H), 4.20 (app t, *J* = 7.3 Hz, 2H), 3.17 (t, *J* = 8.0 Hz, 2H), 2.28 (app quintet, *J* = 7.3 Hz, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 161.2, 159.6, 149.3, 134.3, 127.0, 126.6, 126.4, 120.7, 46.7, 32.7, 19.7.

R_f 0.31 (2% MeOH/EtOAc).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{11}H_{11}N_2O$: 187.0871; found: 187.0875.

6,7,8,9-Tetrahydro-11H-pyrido[2,1-b]quinazolin-11-one (**3**)

33 (133 mg, 0.523 mmol) was cyclised according to general procedure B. Purification by FCC (1% MeOH/CH_2Cl_2) gave **3** (96.2 mg, 0.481 mmol, 92%) as a white amorphous solid; mp 81–83 °C.

IR (neat, ν_{max}) 3373, 2949, 1654, 1613, 1588, 1566, 1476, 1398 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.19 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.65 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.36 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H), 4.02 (t, *J* = 6.2 Hz, 2H), 2.94 (t, *J* = 6.6 Hz, 2H), 1.99–1.93 (m, 2H), 1.92–1.87 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 162.2, 154.9, 147.4, 134.2, 126.6, 126.4, 126.1, 120.5, 42.3, 32.0, 22.2, 19.4.

R_f 0.47 (5% MeOH/CH_2Cl_2).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}N_2O$: 201.1022; found: 201.1014.

Data is in agreement with a reported example.[13]

2,3-Dihydropyrrolo[1,2-a]quinazolin-5(1H)-one (**4**)

7 (987 mg, 4.10 mmol) was cyclised according to general procedure B, and after FCC (3% MeOH/CH_2Cl_2) the title compound **4** (524 mg, 2.81

mmol, 69%) was obtained as a white amorphous solid; mp 213–216 °C, lit. 217–218 °C.

IR (neat, ν_{max}): 3059, 2953, 2925, 2897, 1634, 1593, 1533, 1501, 1461, 1420, 778 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 8.25 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.66 (ddd, *J* = 8.4, 7.3, 1.5 Hz, 1H), 7.40 (ddd, *J* = 8.1, 7.3, 0.9 Hz, 1H*J*), 7.17 (d, *J* = 8.2 Hz, 1H), 4.22 (app t, *J* = 7.4 Hz, 2H), 3.15 (app t, *J* = 7.8 Hz, 2H), 2.41–2.36 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 170.3, 166.5, 138.8, 133.7, 128.9, 125.9, 118.9, 114.6, 48.8, 32.9, 18.7.

R_f 0.17 (5% MeOH/$C1_2Cl_2$).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{11}H_{11}N_2O$: 187.0866; found: 187.0870.

2-(4-Chlorobutanamido)benzamide (**7**)

Anthranilamide (4.95 g, 36.4 mmol) and 4-chlorobutanoyl chloride (6.17 g, 43.7 mmol) were reacted according to general procedure A. Purification by FCC (gradient 50% EtOAc/hexanes to 5% MeOH/EtOAc) gave **7** (8.08 g, 33.6 mmol, 92%) as an off-white amorphous solid; mp 117–119 °C, lit. 114–115 °C;[12]

IR (neat, ν_{max}): 3400, 3270, 3254, 3221, 1669, 1667, 1615, 1591, 1578, 1519, 757 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 11.24 (s, NH, 1H), 8.61 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.49 (dt, *J* = 8.1, 0.8 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.32 (br, NH, 1H), 5.88 (br, NH, 1H), 3.65 (t, *J* = 6.4 Hz, 2H), 2.60 (t, *J* = 7.1 Hz, 2H), 2.20 (quint., *J* = 6.8 Hz, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 171.4. 170.8, 140.2, 133.5, 127.4, 122.9, 121.7, 118.7, 44.4, 35.2, 28.1.

R_f 0.36 (50% EtOAc/hexanes).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{11}H_{14}N_2O_2{}^{35}Cl$: 241.0744; found: 241.0744.

The data was in agreement with a reported example.[12]

2-(4-Chlorobutanamido)-3-methylbenzamide (**8**)

2-Amino-3-methylbenzamide (90.0 mg, 0.599 mmol) was reacted with 4-chlorobutanoyl chloride according to general procedure A. Purification by FCC (100% EtOAc) gave the title compound **8** (59.8 mg, 0.235 mmol, 39%) as a white amorphous solid; mp 145–146 °C.

IR (neat, ν_{max}): 3377, 3291, 3190, 1652, 1588, 1513, 1395 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 8.97 (s, NH, 1H), 7.34–7.32 (m, 2H), 7.16 (t, *J* 7.6 Hz, 2H), 6.21 (br, NH, 1H), 5.63 (br, NH, 1H), 3.64 (t, *J* 6.3 Hz, 2H), 2.58 (t, *J* 7.0 Hz, 2H), 2.24 (s, 3H), 2.21–2.16 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 171.2, 171.0, 136.7, 134.6, 134.1, 129.7, 126.3, 125.0, 44.5, 33.8, 28.3, 19.1.

R_f 0.50 (50% EtOAc/hexanes)

HRMS (ESI+): *m/z* $[M+Na]^+$ calcd for $C_{12}H_{15}N_2O_2{}^{35}Cl^{23}Na$: 277.0714; found: 277.0709.

9-Methyl-2,3-dihydropyrrolo[1,2-a]quinazolin-5(1H)-one (**19**)

8 (42.8 mg, 0.168 mmol) was cyclised according to general procedure B. Purification by FCC (4% MeOH/CH_2Cl_2) gave **19** (17.9 mg, 0.0894 mmol, 53%) as a white amorphous solid; mp 247–250 °C.

IR (neat, ν_{max}): 1632, 1586, 1549, 1481, 1411, 785 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 8.19 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.39 (d, *J* 7.3 = Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 4.66 (app t, *J* = 7.2 Hz, 2H), 3.07 (t, *J* = 8.0 Hz, 2H), 2.73 (s, 3H), 2.32–2.27 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 167.8, 138.7, 137.7, 127.6, 125.9, 124.8, 120.3, 54.1, 32.7, 22.6, 19.7.

R_f 0.14 (4% MeOH/CH_2Cl_2).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}N_2O$: 201.2028; found: 201.1020.

7-Chloro-1,2,3,4-tetrahydro-6H-pyrido[1,2-a]quinazolin-6-one (**39**)

35 (324 mg, 1.12 mmol) was cyclised according to general procedure B. Purification by FCC (5% MeOH/CH_2Cl_2) gave the desired product **39** (133 mg, 0.567 mmol, 51%) and isomer **42** as white amorphous powders; mp 223–225 °C.

IR (neat, ν_{max}): 3064, 2949, 2883, 1660, 1587, 1552, 1458 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.50 (t, *J* = 7.8 Hz, 1H), 7.37 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 3.98 (app t, *J* = 6.3 Hz, 2H), 2.98 (app t, *J* = 6.6 Hz, 2H), 2.17–2.13 (m, 2H), 1.96–1.92 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 166.2, 160.5, 143.5, 135.8, 132.6, 128.8, 117.6, 112.8, 47.4, 32.8, 22.8, 19.1.

R_f 0.33 (6% MeOH/ CH_2Cl_2).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_{12}N_2O^{35}Cl$: 235.0633; found: 235.0623.

7,8,9,10-Tetrahydroazepino[2,1-b]quinazolin-12(6H)-one (**41**)

34 (96.5 mg, 0.360 mmol) was cyclised according to general procedure B. Purification by FCC (4% MeOH/CH_2Cl_2) gave the product **41** (40.2 mg, 0.188 mmol, 52 %) as a white amorphous powder.

IR (neat, ν_{max}): 2921, 2855, 1660, 1587, 1568, 1473, 1393 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 8.25 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.70 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1H), 7.60 (dd, *J* = 8.3, 0.6 Hz, 1H), 7.43 (ddd, *J* = 7.9, 7.2, 1.1 Hz, 1H), 4.40–4.38 (m, 2H), 3.08–3.06 (m, 2H), 1.88–1.81 (m, 6H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 162.1, 159.9, 147.6, 134.3, 127.2, 126.9, 126.5, 120.4, 43.0, 37.9, 29.7, 28.3, 25.6.

R_f 0.38 (4% MeOH/CH_2Cl_2).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{13}H_{15}N_2O$: 215.1184; found: 215.1180.

1-Chloro-6,7,8,9-tetrahydro-11H-pyrido[2,1-b]quinazolin-11-one (**42**)

Side-product **42** was obtained from the cyclisation of **35** as a white amorphous solid (113 mg, 0.538 mmol, 48%); mp 124–127 °C.

IR (neat, ν_{max}): 2949, 2883, 1660, 1587, 1552, 1458 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.54 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.40 (dd, *J* = 7.8, 1.2 Hz, 1H), 4.02 (app t, *J* = 6.0 Hz, 2H), 2.97 (app t, *J* = 6.6 Hz, 2H), 2.03–1.97 (m, 2H), 1.95–1.91 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 160.3, 155.9, 149.6, 134.0, 133.7, 129.0, 125.7, 117.6, 42.8, 31.9, 22.3, 19.3.

R_f 0.47 (EtOAc).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}N_2O^{35}Cl$: 235.0638; found: 235.0641.

5-Chloro-2-(4-chlorobutyl)quinazolin-4(3H)-one (**42a**)

Side-product **42a** (7.0 mg, 0.0258 mmol, 9%) was obtained from quenching the cyclisation of **35** with ^{t}BuOK after one hour and purification by FCC (50% MeOH/hexanes) as a white amorphous solid; decomposition 215 °C.

IR (neat, ν_{max}): 3174, 3037, 2962, 2901, 1679, 1619, 1594, 1457, 817 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 11.71 (s, NH), 7.63–7.59 (m, 2H), 7.46 (dd, *J* = 6.8, 2.1 Hz, 1H), 3.61 (t, *J* = 6.6 Hz, 2H), 2.81 (t, *J* = 7.7 Hz, 2H), 2.09–2.03 (m, 2H), 1.97–1.92 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 161.7, 155.9, 151.0, 133.4, 133.2, 128.4, 125.8, 117.0, 43.5, 33.8, 31.1, 23.6.

R_f 0.36 (50% EtOAc/hexanes).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_{13}N_2O^{35}Cl_2$: 271.0399; found: 271.0387.

1-Chloro-7,8,9,10-tetrahydroazepino[2,1-b]quinazolin-12(6H)-one (**43**)

36 (13.0 mg, 0.0456 mmol, 1.0 eq.) was cyclised according to general procedure B. Purification by preparative TLC (4% MeOH/CH_2Cl_2) gave the product **43** (2.3 mg, 0.00925 mmol, 20%) as a white amorphous powder.

IR (neat, ν_{max}): 2919, 2851, 1664, 1595, 1548, 1457 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.55 (t, *J* = 7.9 Hz, 1H), 7.50 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.42 (dd, *J* = 7.7, 1.3 Hz, 1H), 4.36–4.35 (m, 2H), 3.04–3.02 (m, 2H), 1.90–1.79 (m, 6H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 160.6, 160.2, 150.0, 134.4, 133.7, 129.3, 126.3, 117.6, 43.1, 37.8, 29.7, 28.1, 25.5.

R_f 0.27 (4% MeOH/CH_2Cl_2).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{13}H_{14}N_2O^{35}Cl$: 249.0795; found: 249.0797.

5-Chloro-2-(5-chloropentyl)quinazolin-4(3H)-one (**43a**)

43a (13.0 mg, 0.0456 mmol, 95%) was obtained from quenching the cyclisation of **36** (14.5 mg, 0.0478 mmol) with ^{t}BuOK after 24 hours and purification by FCC (2% MeOH/CH_2Cl_2) as a white amorphous solid; mp 160–161 °C.

IR (neat, ν_{max}): 2956, 2932, 2902, 2869, 1674, 1617, 1600, 1462, cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 11.91 (s, NH), 7.64–7.60 (m, 2H), 7.46 (dd, *J* = 6.8, 2.1 Hz, 1H), 3.56 (t, *J* = 6.5 Hz, 2H), 2.80 (app t, *J* = 7.9 Hz, 2H), 1.97–1.92 (m, 2H), 1.90–1.85 (m, 2H), 1.65–1.60 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 162.8, 157.4, 152.1, 134.3, 134.1, 129.3, 126.7, 118.0, 44.9, 35.6, 32.3, 26.69, 26.67.

R_f 0.37 (2% MeOH/CH_2Cl_2).

HRMS (ESI+): *m/z* $[M+Na]^+$ calcd for $C_{13}H_{14}N_2O^{35}Cl_2Na$: 307.0375; found: 307.0369.

(E)-3-Benzylidene-2,3-dihydropyrrolo[1,2-a]quinazolin-5(1H)-one (**44**)

Adapted from a literature protocol,[25] to a solution of **4** (59.2 mg, 0.318 mmol, 1.0 eq.) in AcOH (1.00 mL) was added benzaldehyde (65.7 µL, 0.350 mmol, 1.1 eq.) then sodium acetate (21.0 mg, 0.260 mmol, 0.8 eq.). The reaction was heated at reflux for four hours, cooled to room temperature, then the solids were filtered, and washed with H_2O, CH_2Cl_2, and EtOH successively, giving **52** (82.9 mg, 0.302 mmol, 95%) as a white amorphous solid; mp 290–293 °C.

IR (neat, ν_{max}): 1634, 1598, 1538, 1493, 1465, 1426, 1139, 757, 688 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 8.27 (d, *J* = 7.8 Hz, 1H), 7.93 (s, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.41–7.32 (m, 3H), 7.20 (d, *J* = 8.3 Hz, 1H), 4.30 (t, *J* = 7.0 Hz, 2H), 3.38–3.37 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 170.5, 161.4, 138.9, 135.3, 133.8, 133.5, 130.2, 129.5, 129.03, 128.97, 126.3, 119.9, 114.5, 46.3, 25.4.

R_f 0.25 (4% MeOH/CH_2Cl_2).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{18}H_{15}N_2O$: 275.1184; found: 275.1176.

(E)-3-(2-Ethylbutylidene)-2,3-dihydropyrrolo[1,2-a]quinazolin-5(1H)-one (**47**)

To a solution of **4** (50.0 mg, 0.269 mmol) in CH_2Cl_2 (920 µL) ^{t}BuOK (36.1 mg, 0.322 mmol, 1.2 eq.) was added, the mixture stirred vigorously for 5 minutes, then 2-ethylbutyraldehyde (33.1 µL, 0.269 mmol, 1.0 eq.) was added. After 1 hour $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were added, the layers separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and excess solvent removed *in vacuo*. Purification by preparative TLC (5% MeOH/CH_2Cl_2) gave the product **47** (49.8 mg, 0.186 mmol, 69%) as an off-white amorphous solid; decomposition 113–115 °C.

IR (neat, ν_{max}): 2958, 2929, 2874, 2857, 1637, 1626, 1598, 1532, 1496, 1461, 1423, 741 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 8.31 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.66 (dt, *J* = 7.4, 1.6 Hz, 1H), 7.41 (dt, *J* = 7.4, 0.8 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 6.92 (dt, *J* = 10.8, 2.7 Hz, 1H), 4.20 (t, *J* = 7.4 Hz, 2H), 3.02 (m, 2H), 2.19-2.14 (m, 1H), 1.61-1.50 (m, 2H, 1.42-1.34 (m, 2H), t, *J* = 7.8 Hz, 6H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 170.6, 160.3, 142.4, 139.0, 133.7, 131.4, 129.0, 126.1, 119.9, 114.3, 45.8, 44.3, 27.7, 23.2, 12.1.

R_f 0.30 (4% MeOH/CH_2Cl_2).

HRMS (ESI+): *m/*z calcd for $C_{17}H_{21}N_2O$: 269.164; found: 269.1658.

(E)-6-chloro-3-((tetrahydro-2H-pyran-4-yl)methylene)-2,3-dihydropyrrolo[1,2-a]quinazolin-5(1H)-one (**50**)

To a solution of **28** (50.0 mg, 0.227 mmol, 1.0 eq) in CH_2Cl_2 (920 µL) ^{t}BuOK (30.5 mg, 0.272 mmol, 1.2 eq.) was added, the mixture stirred vigorously for 5 minutes, then tetrahydro-2*H*-pyrane-4-carbaldehyde (0.250 mmol, 1.1 eq.) was added. After 1 hour $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were added, the layers separated, and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and excess solvent removed *in vacuo*. Purification by preparative TLC (5% MeOH/CH_2Cl_2) gave the product **50** (48.4 mg, 0.153 mmol, 67%) as an off-white amorphous solid; decomposition 211–214 °C.

IR (neat, ν_{max}): 2931, 2832, 1645, 1602, 1585, 1543, 1488 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.52 (t, *J* = 8.1 Hz, 1H), 7.41 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.08 (dd, *J* = 8.3, 0.7 Hz 1H), 6.98 (dt, *J* = 9.7, 2.8 Hz, 1H), 4.19 (t, *J* = 7.3 Hz, 2H), 4.01 (dt, *J* = 11.5, 3.4 Hz, 2H), 3.50–3.45 (m, 2H), 3.06 (dt, *J* = 7.3, 2.8 Hz, 2H), 2.59–2.53 (m, 1H), 1.66–1.62 (m, 4H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 168.1, 159.5, 141.2, 140.5, 136.6, 133.0, 130.0, 129.1, 116.9, 113.2, 67.3, 46.5, 36.6, 31.3, 22.6.

R_f 0.33 (5% MeOH/CH_2Cl_2).

HRMS (ESI+): *m/*z calcd for $C_{17}H_{18}N_2O_2{}^{35}Cl$: 317.1052; found: 317.1056.

(E)-3-((Dimethylamino)methylene)-2,3-dihydropyrrolo[1,2-a]quinazolin-5(1H)-one **(51)**

To a solution of **4** (372 mg, 2.00 mmol, 1.0 eq) in DMF (6.7 mL) was added was added $POCl_3$ (373 µL, 4.00 mmol, 2.0 eq.). Purification by FCC (4% MeOH/CH_2Cl_2) gave **51** (357 mg, 1.48 mmol, 74%) as a tan amorphous solid; decomposition 251–252 °C.

IR (neat, ν_{max}): 1646, 1622, 1598, 1514, 1495, 1397, 1373, 1314, 1109, 776 cm^{-1}.

^1H NMR (600 MHz, d_6-DMSO): δ 7.92 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.64 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H), 7.39 (t, *J* = 1.2 Hz, 1H), 7.27 (dt, *J* = 7.5, 0.6 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 4.10–4.08 (m, 2H), 3.21 (t, *J* = 7.8 Hz, 2H), 3.09 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 168.2, 163.9, 144.0, 139.5, 132.9, 127.1, 123.4 , 118.8, 114.2, 94.5, 45.4, 40.0, 22.7.

R_f 0.21 (5% MeOH/CH_2Cl_2).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{14}H_{16}N_3O$: 242.1293; found: 242.1295.

(E)-3-(Piperidin-1-ylmethylene)-2,3-dihydropyrrolo[1,2-a]quinazolin-5(1H)-one (**52**)

To a solution of **4** (59.0 mg, 0.317 mmol, 1.0 eq.) in CH_2Cl_2 (1.00 mL) was added 1-formylpiperazine (107 µL, 0.951 mmol, 3.0 eq.) and $POCl_3$ (59.1 µL, 0.634 mmol, 2.0 eq.). The reaction mixture was refluxed for 28 hours, cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and quenched with $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (5 ×

10 mL), the combined layers dried over $MgSO_4$, and solvent removed *in vacuo*. Purification by FCC (2% MeOH/CH_2Cl_2 to 5% MeOH/CH_2Cl_2) gave the title compound **52** (28.9 mg, 0.103 mmol, 32%) as a tan amorphous solid.

IR (neat, ν_{max}): 2934, 2853, 1643, 1600, 1587, 1510, 1486, 1439, 1402 cm^{-1}.

^1H NMR (600 MHz, d_6-DMSO): δ 7.93 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.64 (ddd, *J* = 8.4, 7.8, 1.2 Hz, 1H), 7.40 (s, 1H), 7.27 (dt, *J* = 7.8, 0.6 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 4.11 (app t, *J* = 7.8 Hz, 2H), 3.47–3.45 (m, 4H), 3.11 (app t, *J* = 7.8 Hz, 2H), 1.63–1.57 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 164.1, 142.4, 139.5, 132.9, 127.2, 123.4, 118.8, 114.2, 93.9, 50.9, 45.5, 26.1, 23.6, 23.2.

R_f 0.30 (5% MeOH/CH_2Cl_2).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{17}H_{20}N_3O$: 282.1606; found: 282.1615.

(E)-3-(Morpholinomethylene)-2,3-dihydropyrrolo[1,2-a]quinazolin-5(1H)-one (**53**)

To a solution of **4** (50.0 mg, 0.269 mmol, 1.0 eq.) in CH_2Cl_2 (1.35 mL) was added morpohline-4-carbaldehyde (310 mg, 2.69 mmol, 10.0 eq.) and $POCl_3$ (50.1 μL, 0.538 mmol, 2.0 eq.). The reaction mixture was refluxed for three hours, diluted with CH_2Cl_2 (10 mL) cooled to room temperature, and quenched with $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 15 mL), the combined layers dried over Na_2SO_4, and solvent removed *in vacuo*. Purification by FCC (5% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2) gave the title compound **53** (26.7 mg, 0.0942 mmol, 35%) as a tan amorphous solid; decomposition 275 °C.

IR (neat, ν_{max}) 2961, 2925, 2887, 1634, 1600, 1594, 1525, 1510, 1110, 760 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 8.29 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.65 (s, 1H), 7.59 (ddd, *J* = 8.3, 7.4, 1.6 Hz, 1H), 7.32 (ddd, *J* = 8.0, 7.5, 0.9 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 4.14–4.11 (m, 2H), 3.76–3.75 (m, 4H), 3.51–3.48 (m, 4H), 3.50 (d, *J* = 4.8 Hz, 2H), 3.18 (ddd, *J* = 8.3, 6.7, 1.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 164.4, 143.0, 139.5, 133.2, 128.9, 124.5, 119.4, 113.3, 95.6, 66.7, 50.4, 45.0, 24.0.

R_f 0.25 (5% MeOH/CH_2Cl_2).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{18}N_3O_2$: 284.1399; found: 284.1396.

(E)-3-((4-Ethylpiperazin-1-yl)methylene)-2,3-dihydropyrrolo[1,2-a]quinazolin-5(1H)-one (**54**)

To a solution of **51** (50.0 mg, 0.207 mmol, 1.0 eq) in EtOH (1 mL) was added 1-ethylpiperazine (80.0 μL, 0.630 mmol, 0.33 eq) and *N,N*-dimethylaminopyridine (2.5 mg, 0.020 mmol, 0.1 eq), and heated at reflux for 32 hours. The solvent was removed *in vacuo* and purification by FCC (5% MeOH/DCM) gave the product **54** (39.6 mg, 0.128 mmol, 62%) as a pale brown amorphous solid; mp 165–168 °C.

IR (neat, ν_{max}): 2970, 2901, 2819, 1645, 1613, 1598, 1588, 1509, 1491 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 8.27 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.65 (s, 1H), 7.57 (dd, *J* = 8.4, 7.4, 1.5 Hz, 1H), 7.29 (dt, *J* = 7.8, 0.6 Hz, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 4.10 (app t, *J* = 7.8 Hz, 2H), 3.52 (app t, *J* = 5.0 Hz, 4H), 3.16 (dt, *J* = 7.8, 1.2 Hz, 2H), 2.51 (app t, *J* = 4.8 Hz, 4H), 2.46 (q, *J* = 7.2 Hz, 2H), 1.10 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 170.3, 164.6, 142.9, 139.6, 133.1, 128.9, 124.3, 119.5, 113.2, 94.7, 52.8, 52.4, 50.3, 45.9, 24.0, 12.0.

R_f 0.30 (5% MeOH/CH_2Cl_2).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{18}H_{23}N_4O$: 311.1861; found: 311.1866.

(E)-3-((4-Methyl-1,4-diazepan-1-yl)methylene)-2,3-dihydropyrrolo[1,2-a]quinazolin-5(1H)-one (**55**)

To a solution of **51** (21.0 mg, 0.0870 mmol) in EtOH (0.5 mL) was added 1-methylhomopiperazine (32 μL, 0.257 mmol, 3.4 eq), and *N,N*-dimethylaminopyridine (1.1 mg, 0.0087 mmol, 0.1 eq), and heated at reflux for 96 hours. The solvent was removed *in vacuo* and purification by FCC (5% MeOH/CH_2Cl_2) gave the product **55** (13.2 mg, 0.0425 mmol, 49%) as a pale brown amorphous solid; mp 92–94 °C.

IR (neat, ν_{max}): 2939, 2913, 2857, 2810, 1641, 1602, 1587, 1506, 1496 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.27 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.74 (t, *J* = 1.5 Hz, 1H), 7.57 (ddd, *J* = 8.3, 7.3, 1.5 Hz, 1H), 7.29 (ddd, *J* = 8.1, 7.5, 1.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 4.11–4.07 (m, 2H), 3.62 (t, *J* = 6.3 Hz, 2H), 3.59–3.57 (m, 2H), 3.21 (m, 2H), 2.67–2.65 (m, 2H), 2.61–2.59 (m, 2H), 2.39 (s, 3H), 1.95–1.91 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 164.6, 144.5, 139.7, 133.0, 128.8, 124.1, 119.5, 113.1, 94.1, 59.1, 57.0, 54.1, 51.7, 46.9, 45.8, 28.5, 23.9.

R_f 0.32 (10% MeOH/CH_2Cl_2 + 1% NH_4OH).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{18}H_{23}N_4O$: 311.1872; found: 311.1884.

Tert-Butyl (E)-4-((5-oxo-1,2-dihydropyrrolo[1,2-a]quinazolin-3(5H)-ylidene)methyl)piperazine-1-carboxylate (**56**)

To a solution of **51** (21.0 mg, 0.0870 mmol) in EtOH (0.5 mL) was added with 1-boc-piperazine (49.0 mg, 0.263 mmol, 3.0 eq) and *N,N*-dimethylaminopyridine (1.1 mg, 0.0087 mmol, 0.1 eq), and heated at reflux for 96 hours. The solvent was removed *in vacuo* and purification by FCC (5% MeOH/CH_2Cl_2) gave the product **56** (20.0 mg, 0.0522 mmol, 60%) as a pale brown amorphous solid; decomposition 140 °C.

IR (neat, ν_{max}): 2974, 2918, 1688, 1644, 1605, 1591, 1518, 1494, 1405 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 8.24 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.57 (m, 1H), 7.54 (ddd, *J* = 8.4, 7.4, 1.4 Hz, 1H), 7.27 (dt, *J* = 7.9, 0.6 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 4.07 (app t, *J* = 7.9 Hz, 2H), 3.48–3.46 (m, 4H), 3.39 (br, 4H), 3.10 (dt, *J* = 7.8, 1.4 Hz, 2H), 1.46 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 170.2, 164.3, 154.5, 142.5, 139.5, 133.0, 128.6, 124.2, 119.4, 113.4, 95.8, 80.8, 46.0, 28.6, 24.0. * C13 and C14 were weak and very broad in ^{13}C NMR and could not be reliably assigned.

R_f 0.25 (5% MeOH/CH_2Cl_2).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{21}H_{27}N_4O_3$: 383.2078; found: 383.2070.

(E)-7-Chloro-4-((dimethylamino)methylene)-1,2,3,4-tetrahydro-6H-pyrido[1,2-a]quinazolin-6-one (**57**)

To a stirred solution of **40** (88.0 mg, 0.37 mmol, 1.0 eq.) in DMF (740 μL) was added $POCl_3$ (69.9 μL, 0.74 mmol, 2.0 eq.) and the reaction was heated to 60 °C for 6 hours. The reaction was cooled to room temperature, diluted with CH_2Cl_2 (15 mL), and quenched with $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 15 mL), the combined organic layers dried over Na_2SO_4 and solvent removed *in vacuo*. The residue was co-evaporated with toluene (3 × 5 mL) and purification by FCC (6% MeOH/CH_2Cl_2) gave the product **57** (52.0 mg, 0.18 mmol, 49%) as a yellow amorphous solid; mp 197–200 °C.

IR (neat, ν_{max}): 3111, 2944, 2885, 2813, 1607, 1587, 1499, 1481, 1464 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.39 (t, *J* = 8.2 Hz, 1H), 7.29 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.14 (dd, *J* = 8.5, 0.6 Hz, 1H), 3.85 (app t, *J* = 6.0 Hz, 2H), 3.12 (s, 6H), 2.73–2.71 (m, 2H), 2.09–2.05 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 168.9, 158.6, 151.1, 144.4, 135.2, 131.2, 127.0, 117.7, 111.7, 94.2, 46.9, 43.8, 23.4 , 22.5.

R_f 0.43 (6% MeOH/CH_2Cl_2).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{15}H_{17}N_3O^{35}Cl$: 290.1055; found: 290.1048.

(E)-7-Chloro-4-((4-methylpiperazin-1-yl)methylene)-1,2,3,4-tetrahydro-6H-pyrido[1,2-a]quinazolin-6-one (**58**)

To a solution of **57** (26.0 mg, 0.09 mmol, 1.0 eq.) in EtOH (450 µL) in a microwave vial was added 1-methylpiperazine (49.7 µL, 0.45 mmol, 5.0 eq.) and DMAP (1.1 mg, 0.009 mmol, 0.1 eq.). The vial was sealed and the reaction heated at 70 °C for 6 hours, then cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL), the combined organic layers dried over Na_2SO_4, and excess solvent was removed *in vacuo*. Purification by FCC (10% MeOH/CH_2Cl_2 + 0.5% NH_4OH) gave the product **58** (27.6 mg, 0.080 mmol, 89%) as a yellow amorphous solid; mp 174–177 °C.

IR (neat, ν_{max}): 2934, 2845, 2790, 1615, 1586, 1494, 1474, 1419 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.39 (t, *J* = 8.2 Hz, 1H), 7.28 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 3.85 (app t, *J* = 6.0 Hz, 2H), 3.53 (m, 4H), 2.60 (app t, *J* = 6.1 Hz, 2H), 2.43 (m, 4H), 2.30 (s, 3H), 2.08 (app quintet, *J* = 6.0 Hz, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 165.9, 158.3, 149.3, 144.2, 135.1, 131.7, 127.0, 117.7, 111.7, 94.8, 55.2, 51.2, 46.7, 46.2, 24.2, 22.3.

R_f 0.22 (10% MeOH/CH_2Cl_2 + 0.5% NH_4OH).

HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{18}H_{22}N_4O^{35}Cl$: 345.1482; found: 345.1494.

Acknowledgment

Charlotte Sutherell was funded by the Cambridge PhD Training Programme in Chemical Biology and Molecular Medicine. We gratefully acknowledge the EPSRC (SVL, Grant Nos. EP/K099494/1 and EP/K039520/1).

Supporting Information

Additional synthetic methods, characterization data, synthesis of starting materials, and NMR spectra.

Primary Data

Primary data related to this publication (NMR files, processed NMR spectra, IR files, IR pdf files) is available at http://dx.doi.org/10.17863/CAM.523 .

References

(1) Department of Chemistry, Imperial College, London, SW7 2AZ.
(2) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem Rev* **2003**, *103*, 893–930.
(3) Connolly, D. J.; Cusack, D.; Sullivan, T. P. O.; Guiry, P. J. *Tetrahedron* **2005**, *61* (737), 10153–10202.
(4) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62* (771), 9787–9826.
(5) Johns, S; Lamberton, J. A.. *J. Chem. Soc., Chem. Commun.* **1965**, 267.
(6) Fitzgerald, J. S.; Johns, S. R.; Lamberton, J. A.; Redcliffe, A. H. *Aust. J. Chem.* **1966**, *19*, 151–159.
(7) Cho, J.; Bae, S.; Kim, H.; Lee, M.; Choi, Y.; Jin, B.; Lee, H. J.; Jeong, H. Y.; Lee, Y. G.; Moon, J. *J. Agric. Food Chem.* **2015**, *63*, 3587–3592.
(8) Moehrle, H.; Hemmerling, H. J. *Arch. der Phamazie* **1978**, *311*, 586–594.
(9) Hassanzadeh, F.; Jafari, E.; Hakimelahi, G. H.; Rahmani, M.; Khajouei; Jalali, M.; Khodarahmi, G. A. *Res Pharm Sci* **2012**, *7* (87-94).
(10) Sutherell, C. L.; Tallant, C.; Monteiro, O. P.; Yapp, C.; Fuchs, J. E.; Fedorov, O.; Siejka, P.; Müller, S.; Knapp, S.; Brenton, J. D.; Brennan, P. E.; Ley, S. V. *J Med Chem* **2016**, *57*, 5095-5101.
(11) Nazarenko, K. G.; Shyrokaya, T. I.; Tolmachev, A. A. *Synth. Commun.* **2008**, *33* (2), 303–310.
(12) Dunn, A. D.; Kinnear, K. I. *J. Heterocycl. Chem.* **1986**, *23* (3), 53–57.
(13) Sun, X.; Hu, Y.; Nie, S.; Yan, Y.; Zhang, X. *Adv. Synth. Catal.* **2013**, *355* (11-12), 2179–2184.
(14) Jones, A. M.; Lebl, T.; Patterson, S.; van Mourik, T.; Früchtl, H. A.; Philp, D.; Slawin, A. M. Z.; Westwood, N. J. *Tetrahedron* **2009**, *65* (2), 563–578.
(15) Zhu, Y.; Fei, Z.; Liu, M.; Jia, F.; Wu, A. *Org. Lett.* **2013**, *15* (2), 378–381.
(16) Moorthy, J. N.; Senapati, K.; Parida, K. N.; Jhulki, S.; Sooraj, K.; Nair, N. N. *J. Org. Chem.* **2011**, *76* (23), 9593–9601.
(17) Cheng, X.; Vellalath, S.; Goddard, R.; List, B. *J. Am. Chem. Soc.* **2008**, *130* (47), 15786–15787.
(18) Tu, T.; Wang, Z.; Liu, Z.; Feng, X.; Wang, Q. *Green Chem.* **2012**, *14* (4), 921–924.
(19) Möhrle, H.; Seidel, C.-M. *Arch. der Phamazie* **1976**, *309*, 542–550.
(20) Elmuradov, B. Z.; Abdurazakov, A. S.; Shakhidoyatov, K. M. *Chem. Nat. Compd.* **2008**, *44* (4), 475–479.
(21) Il'chenko, A. Y.; Nazarenko, K. G.; Shirokaya, T. I.; Tolmachev, A. A.; Tolmachev, A. I. *Ukr. Khimicheskii Zhurnal (Russian Ed.* **2003**, *69*, 48–55.
(22) Bubenyák, M.; Pálfi, M.; Takács, M.; Béni, S.; Szökó, E.; Noszál, B.; Kökösi, J. *Tetrahedron Lett.* **2008**, *49*, 4937–4940.
(23) Voitenko, Z. V.; Halaev, O. I.; Samoylenko, V. P.; Kolotilov, S. V.; Lepetit, C.; Donnadieu, B.; Chauvin, R. *Tetrahedron* **2010**, *66* (41), 8214–8222.
(24) Darras, F. H.; Kling, B.; Heilmann, J.; Decker, M. *ACS Med. Chem. Lett.* **2012**, *3* (11), 914–919.
(25) Yan, J. W.; Li, Y. P.; Ye, W. J.; Chen, S. Bin; Hou, J. Q.; Tan, J. H.; Ou, T. M.; Li, D.; Gu, L. Q.; Huang, Z. S. *Bioorganic Med. Chem.* **2012**, *20* (8), 2527–2534.